HYPOTHESIS

THE TIMING OF PEDIATRIC IMMUNIZATION AND THE RISK OF INSULIN-DEPENDENT DIABETES MELLITUS

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INSULIN-DEPENDENT DIABETES mellitus (IDDM) is believed to be an autoimmune disease induced by a variety of environmental stimuli [1]. Vaccines and infectious agents have been suggested to have an influence, but most of this research has centered on the ability of these agents to infect the pancreatic islet cells or contain antigens that mimic autoantigens. Nonobese diabetic (NOD) mice and BioBreeding (BB) rats spontaneously develop IDDM and are believed to be good models of human disease. Classen [2] found that administration of the diphtheria-tetanus-pertussis (DTP) and anthrax vaccines to NOD mice and BB rats at birth prevented the development of diabetes, whereas administration of the DTP vaccine starting at 8 weeks was associated with an increased incidence of diabetes. Therefore, we decided to investigate whether epidemiologic data exist to support a relationship between the timing of vaccination and the development of IDDM in humans.

Materials and Methods

Ecological Studies Correlating Vaccination and the Development of Diabetes

The incidence of type I diabetes was correlated with immunization schedules in all Western European nations except Germany, which has no diabetes registry. Data were limited to the years 1986–1990 except for Iceland and Malta, which have small populations and reported the incidence during a multiyear interval. The best estimate of the incidence of diabetes was included if a country had more than one registry. For locations with more than one registry considered of equal quality and reliability, more than one was included in the study. Data from registries included in the EURODIAB Ace study [3] were given preference because of the uniformity of methods used. Cases of IDDM were ascertained according to the following methods.

Sweden [4]. Sweden requires reporting of all cases of IDDM to the central diabetes registry, and all cases were identified prospectively. Ascertainment, verified with data from the Swedish Diabetes Association, is estimated at over 99%.

Finland [5,6]. Before 1987 all cases of IDDM were ascertained from the Finnish Central Drug Registry, which provided free insulin to all diabetics. A prospective registry was started in 1986. In Finland all children with newly diagnosed IDDM are hospitalized for about a week, and records of the admission in each hospital are collected by the study group. Ascertainment is estimated at over 99%.

New Zealand [7]. Patients developing diabetes in Canterbury are prospectively identified using hospital records and records kept by the three specialists who take care of most diabetics in this area. Ascertainment was estimated at over 99% using records from the diabetes association.

Malta [8]. St. Luke's Hospital is the only hospital in Malta caring for type I diabetics, and the hospital records were used to ascertain cases of IDDM. Since the hospital offers free care to all, it is believed that most, but not all, children with type I diabetes are registered with the hospital's clinic. The ascertainment is expected, however, to be significantly under 99%.

Republic of Ireland [9]. New cases of IDDM were reported by pediatricians to the British Paediatric Surveillance Unit. Secondary identification was made through the British Diabetic Association, which contacted nurses caring for diabetics and asked them to

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report new cases. Ascertainment is likely to be less than 90%.

Spain (Madrid) [10]. Retrospective review of hospital records was used as the primary source of data, and membership files of the Spanish Diabetic Association were used as a secondary source for ascertainment, which is estimated at 90%.

Switzerland [11]. All 19-year-old men in Switzerland are required to enlist in the military with the exceptions of those with diabetes and certain other diseases. Data from military records were used to ascertain all male juvenile diabetics surviving to the age of 19 and remaining in Switzerland. No estimate of ascertainment is provided.

Iceland [12]. The primary source for identifying cases of IDDM was prospective hospital records, and the secondary source was the registry of the diabetic association. Ascertainment was assessed through the National Insurance Institution at over 99%.

EURODIAB, all other countries in the study [3]. Primary identification of IDDM cases came from hospital records, and ascertainment was assessed using a variety of secondary sources, including prescription data, insurance data, and diabetes association data. All centers had an ascertainment of 94% or better except Portugal, with 91%.

Immunization practices reported to the World Health Organization (WHO) [13] were used when available, but other references were also used to substantiate the immunization schedule [3,8–20]. WHO records on immunization acceptance were used to verify a high immunization rate with the vaccine. We used WHO records for vaccine penetration because these are generally considered the standard. These data are reported to the WHO by public health officials in the country and are often updated annually. A complete historic record of vaccine uptake is available from the WHO on a spreadsheet file, and the most recent data are available on the Internet at the WHO's homepage (http://www.who.org). The data are periodically published in *WHO Health Statistics Annual.*

Published literature was evaluated to find countries where both immunization practices changed and accurate diabetes registries existed so changes in immunization schedules could be correlated to changes in immunization practice.

Statistics

Statistics were generated from group means using a normal approximation to the Poisson distribution and the Wilcoxon test for determination of trend.

Results

Immunization at birth with Bacille Bilié de Calmette-Guérin Associated with a Reduced Incidence of Diabetes in Sweden

The Bacille bilié de Calmette-Guérin (BCG) vaccine was routinely administered at birth to all newborns until the practice was stopped abruptly in April 1975. A country-wide diabetes registry exists in Sweden allowing one to perform a cohort study observing the incidence of diabetes in those children immunized at birth with BCG and those who were not. Cohort data exist on the incidence of diabetes in children born in the 2 years before discontinuation of BCG immunization, 1973–1974, and in children born in the 2 years following BCG immunization, 1976–1977 [21].

Swedish law until early 1976 required immunization with smallpox vaccine before the age of 5, and the vaccine was administered primarily at 2 months or 9 months of age [22]. Detailed records on the acceptance rates with the smallpox vaccine in the birth cohorts are not available. Swedish public health officials have indicated that the smallpox vaccine was increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of adverse responses from immunization exceeded the risk of infection with smallpox. A decline in the acceptance rate of the smallpox vaccine in Sweden is supported by WHO records indicating that the 948,000, 898,000, and 807,000 doses of smallpox vaccine were administered in 1972, 1973, and 1974, respectively (*WHO Health Statistics Annual*).

Table 1 analyzes the differences in the cumulative incidence of diabetes in children followed from ages 4 to 15 years. The table shows the cumulative incidence in birth cohorts who received BCG, in 1973 and 1974, and those that did not, in 1976 and 1977. If one ignores the confounding effect of the smallpox vaccine and compares the 1973 and 1974 cohort with the 1976 and 1977 cohort, immunization at birth with one dose of BCG is associated with a reduction in 32 cases of diabetes/100,000 individuals. If one compensates for the confounding effect of the smallpox vaccine by comparing the 1974 and 1976 cohorts, then immunization at birth with BCG is associated with the prevention of 48.6 cases of diabetes/100,000 children immunized ($P = .006$, two-tail).

TABLE 1. Birth cohort analysis of insulin-dependent diabetes mellitus

Birth cohort	Cases of diabetes	Cohort size	Cumulative incidence (per 100,000)
1977	320	95,098	336.49
1976	342	97,327	351.39
1974	329	108,671	302.75
1973	345	107,582	320.69

Analysis of cohorts	Difference (per 100,000)	*P* values (normal approximation, Poisson distribution) Two-tail	One-tail
(1976 and 1977) vs. (1974 and 1973)	32.2	.0726	.0363
1974 vs. 1976	48.64	.0057	.0028

Incidence of Diabetes in Western Europe Correlates with Vaccination Practices

The data in Table 2 show that countries where BCG vaccine is given at birth generally have a lower incidence of diabetes, whereas the countries where children receive the BCG vaccine after 2 months of age, most commonly at school age, have an increased incidence of diabetes. Those not receiving the BCG vaccine but receiving the pertussis vaccine generally had an intermediate risk. The findings are highly statistically significant. Finland, Sweden, and Sardinia had incidences of diabetes higher than could be explained by immunization practices.

Addition of Vaccines to the Finnish Immunization Schedule Is Followed by Rises in the Incidence of Diabetes

The incidence of diabetes was stable in the 0–4-year-old age group in Finland from 1966–1975, until after the government made several changes in its vaccination schedule. The addition to the vaccination schedule of new vaccine antigens administered to children older than 2 months of age was followed by rises in the incidence of diabetes that were predictable based on animal models [2]. The government immunized 130,000

TABLE 2. Immunization schedule vs. incidence of type I diabetes mellitus in 0–14 year olds

Group immunization schedule	Year	Cases of diabetes	Annual incidence (per 100,000)	Group mean	*P* values		
No pertussis, no BCG				16.6			
Lombardi region, Italy	1988	193	6.8				
Lazio region, Italy	1987	117	6.5				
Sardinia, Italy	1987	221	30.2				
Sweden	1990	364[a]	23				
Pertussis, BCG before 2 months				7.4	XXXXX		
Republic of Ireland	1988	71	6.8				
France	1990	261	7.8				
Austria	1989	205	7.7				
Portugal	1986	25	7.5				
Switzerland	1985–1987	123	7.2[b]				
Pertussis, no BCG				10.92	0.026	XXXXX	
Iceland	1980–1989	68	10.8				
Netherlands	1989	58	11				
Catalonia, Spain	1986	297	10.6				
Madrid, Spain	1985–1988	501	10.9				
Belgium	1989	31	9.8				
Luxembourg	1989	16	12.4				
Pertussis, BCG vaccination school-aged				19.02	<.0001	0.021	XXXXX
Northern Ireland	1988	130	16.6				
Oxford, England	1988	161	16.4				
Scotland	1988	190	19.8				
Denmark	1990	66	21.5				
Norway	1989	158	20.8				
Malta	1980–1987	90	(13.6+)				
H. influenzae, pertussis, BCG vaccination 0–1 month and school-aged				42.9	<.0001	<.0001	<.0001
Finland	1988	151	42.9				

Note. From health care provider in country. All *P* values calculated comparing the percentage diabetic to that in the group above marked by XXXXX. Statistics were generated using a normal approximation to the Poisson distribution, two-tailed, using T = 1 except in group 3, (0.026) where T = 4. Abbreviation used: BCG, Bacille bilié de Calmette-Guérin.

[a] Approximation.

[b] Derived from birth cohort study.

TABLE 3. Incidence of type I diabetes in Finland

Age group (y)	Years	*n*	Annual incidence (per 100,000)	Increased incidence (%)	*P* value[a]
0–4	1970–1976	262	11.8		
	1977–1979	174	19.3	64	
	1980–1982	152	16	36	
	1987–1989	243	26	120	
	1990–1992	277	29.2	147	
					P <.0001
5–9	1970–1976	729	27.6		
	1977–1979	304	32	16	
	1980–1982	299	33	20	
	1987–1989	382	39.3	42	
	1990–1992	373	38.6	40	
					P <.0001

[a] *P* values calculated using Wilcoxon test for determination of trends.

TABLE 4. Incidence of type I diabetes mellitus, age 0–19 years, Christchurch, New Zealand

Year	Incidence of diabetes (cases per 100,000)	
1982	12.5	
1983	12.5	
1984	13.4 (average incidence 1982–1987, 11.2)	
1985	12.5 (approximate cases of diabetes, 73)	
1986	8.6	
1987	7.6	
1988	9.6 (national hepatitis B immunization program initiated)	*P* = .0008
1989	16.4	
1990	21.4 (average incidence 1989–1991, 18.1)	
1991	16.6 (approximate cases of diabetes, 58)	

Note. *P* value calculated using a normal approximation to the Poisson distribution with T = 3 and a two-tail test.

infants, equivalent to two annual birth cohorts, aged 3 months to 5 years old, with *Haemophilus influenzae* or meningococci polysaccharide vaccines in a vaccine trial in November 1974 [23]. In 1976 the pertussis vaccine was made more antigenic by the addition of a second strain of bacteria [24]. These changes were followed by a 64% rise in IDDM, which occurred in 0–4-year-olds during the years 1977–1979 compared with the years 1970–1976. The vaccine regimen was next altered to include the measles, mumps, rubella vaccine at the ages of 14 months and 6 years in 1982 [25]. A trial of *Haemophilus influenzae* conjugate vaccine initiated in January 1986 included 114,000 children born between October 1, 1985, and August 31, 1987. Based on the results of the trial, the *Haemophilus influenzae* vaccine became part of the standard vaccine schedule in Finland starting in January 1988 [26]. These changes were followed by a 62% rise in the incidence of diabetes in the 0–4-year-old age group and a 19% rise in the 5–9-year-old age group between the years 1980–1982 and 1987–1989 [6,25,27]. The net effect was the addition of three new vaccines to the 0–4-year-old age group and a 147% increase in the incidence of IDDM, the addition of one new vaccine to the 5–9-year-olds and a rise in the incidence of diabetes of 40%, and no new vaccines added to the 10–14-year-olds and a rise in the incidence of IDDM by only 8% between the intervals 1970–1976 and 1990–1992. The rise in IDDM in the different age groups correlated with the number of vaccines given (Table 3).

Incidence of IDDM Rises Dramatically after Hepatitis B Immunization

The incidence of type I diabetes in the 0–19-year-old age group has been studied since 1982 in Christchurch, New Zealand, and a rise in type I diabetes was noted to occur in 1989 [28] after the initiation of an hepatitis B immunization program. The government of New Zealand introduced a massive hepatitis B vaccination program in 1988, which was extended to include all children under 16, and over 70% of children were vaccinated within a few years after the start of the program, with almost all of the immunizations starting after 6 weeks of life. The initial vaccine was a human blood–derived product but was switched to a recombinant vaccine around 1990. The incidence of type I diabetes in persons 0–19 years old living in Christchurch rose from 11.2 cases per 100,000 children annually in the years before the immunization program, 1982–1987, to 18.1 cases per 100,000 children annually ($P = .0008$) in the years following the immunization, 1989–1991, (Table 4). Additional data presented publicly by Dr. Scott show that the increased incidence of diabetes in Christchurch was extended through 1994.

Discussion

Cohort data from Sweden (Table 1) indicated that the administration of one dose of BCG vaccine at birth is associated with a reduction of up to 49 cases of diabetes per 100,000 children immunized. This finding is supported by ecological data (Table 2) from Western Europe. The mean annual incidence of diabetes from ages 0–14 years in a group of countries where children were receiving BCG at birth was 7.4 cases per 100,000 compared with 10.92 cases per 100,000 in a group of countries where children were receiving a similar immunization schedule but lacking BCG. According to the ecological study, the administration of a BCG vaccine at birth is associated with a reduction of 52.8 cases

of diabetes per 100,000 children immunized—(10.92–7.4) × 15 years—which is remarkably similar to the 49 cases seen in the cohort study.

Temporal studies in Finland and New Zealand showed that rises in the incidence of diabetes occurred following the addition of new vaccines, which were administered after 6 weeks of life, to an immunization schedule. Data presented in Table 2 support this finding since countries administering the BCG starting at school age were associated with an increased incidence of diabetes. The potential effect is most striking when comparing the incidence of diabetes in Northern Ireland, where the BCG vaccine is given at school age, to that in the Republic of Ireland, where the BCG vaccine had been given at birth. To verify a causal effect, we entered into a collaboration with Dr. Tuomilehto of the Finnish Public Health Service. In a prospective randomized trial performed in Finland, one group received four doses of Hib vaccine, and a control group received one dose [18]. We found that after an approximate 10-year follow-up, there were 20 more cases of IDDM in the group that received four doses vs. one dose, which may amount to a 7%–10% increase (report in preparation).

Vaccines cannot explain all of the variability in the incidence of IDDM, and changes in other factors beside vaccines may be responsible for the above-described alterations in the incidence of IDDM. Natural infections with agents such as coxsackievirus B [29] and other viruses may be responsible for the yearly variations in the development of diabetes. Social factors altering exposure to natural infections may be responsible for temporal and geographic differences in the incidence of IDDM. These potential effects, including income, population density, hygiene, caesarean birth, and early enrollment in day care, have been reviewed recently [30]. Consumption of milk and changes in breast-feeding [31] have been associated with geographic and temporal differences in the incidence of IDDM. Variation in temperature—in particular, a higher incidence of IDDM in northern compared with southern countries—has been proposed as an explanation for difference in IDDM incidence in different countries [32]; however, yearly changes in temperature may explain annual variations. Genetic predisposition to IDDM—in particular, the presence of high-risk major histocompatibility complex genes—has been cited as an explanation for geographic differences in the incidence of IDDM [33]. Maternal age [34] has been associated with IDDM, and difference in maternal age because of cultural factors and temporal social factors may also explain difference in the incidence of IDDM. Underreporting of cases of IDDM during previous decades and in countries with less-developed public health care systems cannot be ruled out as a cause for differences in the incidence of IDDM.

The immune modulatory actions of vaccines have received little attention; however, the vaccine-induced interferon release may have a significant biologic effect on the incidence of diabetes. Interferon released following immunization at birth may inhibit vertically transmitted coxsackievirus B infections, which have been attributed to causing 27% or more cases of IDDM [29]. Interferon released after the vertically transmitted viral infection has initiated an autoimmune response may actually exacerbate the autoimmune response since interferons have been implicated in exacerbating autoimmunity, including IDDM [35]. It is also possible that immunization later in life causes the release of diabetes-inducing viruses that have chronically infected the host [36].

These studies suggest that the timing of pediatric immunizations may alter the development of IDDM in humans. The results also indicate that previous vaccine trials are flawed because they are not designed to detect associations between vaccination and autoimmune diseases, such as IDDM. Prospective clinical trials are needed to further evaluate the effect of vaccines on IDDM.

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